Synthesis and structural characterization of novel 1,2,3-triazole derivatives of benzoxazole

Robert Ostrički¹, Tatjana Gazivoda Kraljević²

¹Pliva Hrvatska d.o.o., Prilaz baruna Filipovića 25, 10000 Zagreb
²Department of Organic Chemistry, Faculty of Chemical Engineering and Technology
University of Zagreb, Marulićev trg 19, 10000 Zagreb

Background

A great number of deaths are occurring throughout the world because of infectious diseases which are difficult to treat with traditional antibiotics, leaving clinicians depending on limited drugs such as vancomycin. As a consequence, there is an increased demand to develop new antimicrobial agents. Benzoxazoles are structural isosteres of natural nucleotides which interact easily with biopolymers, and represent an important class of heterocyclic compounds exhibiting remarkable pharmacological activities such as antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, antivirucidal and antihistaminic. Furthermore, a number of available marketed drugs posses benzoxazole ring, i.e. nonsteroidal anti-inflammatory drug (NSAID)-flunoxaprofen, benoxaprofen and antibiotic–calcimycin, roxazone. Benzoxazole moieties also act as tyrosinase inhibitor and cholesterol ester transfer protein inhibitor. Increased number of deaths and scarcity of effective traditional antibiotics result in high demand for new, effective antimicrobial agents. Due to its ability to easily interact with biopolymers, benzoxazole arises as a promising scaffold for the synthesis of new, effective antibiotics.

Results

Key precursors for click reaction, propargylated 2-aminobenzoxazole (2) and 2-thiobenzoxazole (14) were prepared in two-step reaction including cyclization reaction of 2-aminophenol using di(imidazole-1-yl)methaneimine (for 1) and carbon disulfide (for 13), and subsequent N-alkylation reaction of 1 and 13 with propargyl bromide as an alkylating reagent.

2-aminobenzoxazole (3-12) and 2-thiobenzoxazole derivatives (15-24) with 1,2,3-triazole moiety were synthesized by Cu(II) catalyzed click reaction of 2-propargylated benzoxazole derivatives (2 and 14) with corresponding azides (Scheme 1).

Formation of the triazole ring is confirmed by the disappearance of the triplet at ~3.2 ppm of the terminal alkyne proton in ¹H-NMR spectra of compounds 2 and 14 (Figure 1) and the appearance of the singlet of the triazole ring proton at ~ 9 ppm in ¹H-NMR spectra of compounds 3-12 and 15-24 (Figure 2).

Conclusion

In order to evaluate in vitro antibacterial activity against Gram-positive and Gram-negative bacteria, novel 1,2,3-triazole derivatives of 2-aminobenzoxazole (3-12) and 2-thiobenzoxazole (15-24) have been synthesized by Cu(II) catalyzed click reaction of propargylated benzoxazole derivatives 2 and 14 with corresponding azides.

Structures of the prepared compounds were confirmed by ¹H and ¹³C-NMR spectroscopy and mass spectrometry as well.

References


Acknowledgements

Financial support from Pliva Hrvatska d.o.o. and Croatian Science Foundation under the project IP-2018-01-4682.